I. Status of Claims

Claims 1-10 and 15-18 were withdrawn.

Claims 18-22 were previously canceled.

Claims 11-14 are pending.

II. Claims 11-14 are not *prima facie* obvious

The Office Action mailed February 26, 2010 rejects claims 11-14 under 35 U.S.C. § 103(a) as being obvious over Hilleman et al. (U.S. Pat. 3,906,092) in view of Wong et al. (*Antimicrobial Agents and Chemotherapy* (1995) 39:2574-76). The Office Action alleges that Hilleman teaches methods of intramuscular administration of a composition comprising influenza vaccine at least twice. The Office Action alleges that Wong teaches administering double stranded RNA (Poly I:C) to the nasal mucosa at least twice. The Office Action further alleges that based on Hilleman and Wong, it would have been *prima facie* obvious to administer a composition comprising influenza vaccine containing influenza virus and double stranded RNA (Poly I:C). Claims 11-14 are not *prima facie* obvious over Hilleman and Wong. One skilled in the art would have no motivation to combine the teachings of Hilleman and Wong. Hilleman teaches away from an aqueous type influenza vaccine comprising a double stranded RNA.

Hilleman teaches away from the use of double stranded RNA (e.g., poly A:U and poly (I:C)) as a useful adjuvant in an aqueous type influenza vaccine. Hilleman describes a method of intramuscularly administering a water-in-oil or oil-in-water emulsion type influenza vaccine preparation comprising an influenza virus antigen and a double stranded RNA (poly I:C) (claims 1-15, Examples 1-6, 12). Examples 1-3 of Hilleman disclose an aqueous type influenza vaccine preparation. Hilleman reports: "[I]ncorporation of **poly A:U** into the *aqueous type vaccine* **completely inhibited the antibody response to all four influenza virus antigens** whether one or two injections were given . . . . [I]ncorporation of **poly I:C** into the *aqueous type vaccine* **neither inhibited nor enhanced antibody response** when compared to the antibody response of recipients of aqueous type vaccine alone." Further, Hilleman reports that "**no antigenic enhancement was given to the aqueous type vaccine by the addition of poly I:C.**" (Column 6, lines 60-61) (emphasis added).

Thus, Hilleman teaches away from the use of a double stranded RNA as a component in an aqueous type vaccine to prevent influenza, to which claims 11-14 are directed. As such, Hilleman cannot be combined with Wong to support a *prima facie* case of obviousness. Withdrawal of the rejection of claims 11-14 under 35 U.S.C. § 103(a) is respectfully requested.

III. Claims 11-14 are nonobvious based on unexpected superior results

Even if Hilleman and Wong could be properly combined in an allegation of *prima facie* obviousness, which Applicants vehemently deny due to the teaching away by Hilleman, claims 11-14 are nonetheless nonobvious due to the finding of unexpected superior results. The Office Action alleges that Wong teaches administering double stranded RNA (poly I:C). Of note, Wong administered *poly (IC·LC)*, not poly (I:C). Poly (IC·LC) has a structure stabilized with poly-L-lysine carboxymethyl cellulose (P.2574, left column, lines 1-3), i.e., the structure contains double stranded RNA as well as a peptide bond and glucoside bond, and is not poly(I:C). Wong further notes that multiple high doses of poly (IC·LC) given i.v. have been known to produce toxic reactions in human (P. 2575, right column, lines 40-41). Nevertheless, Wong discloses a degree of prophylactic efficacy against the influenza virus infection by intranasal or intraperitoneal administration of poly(IC·LC) alone, not in combination with pathogens such as influenza virus antigens. Wong explains that poly (IC·LC) is able to modulate immune responses including interferon induction and activation of natural killer (NK) cells (P. 2575, right column, lines 29-37).

In the method of preventing influenza to claims 11-14 are directed, the mucosally administered vaccine comprising a double stranded RNA and an influenza virus antigen *in combination* has greater effects than merely nonspecific antiviral defense due to induction of interferons and/or NK cells. When administered intranasally in aqueous form, the following additional specific effects are found:

(1) virus specific IgA is efficiently induced on the mucosal surface (Example 1 and Fig. 1),

(2) lethal infection is prevented in a virus challenge test using mouse (Example 1, Fig. 2 and Table 1),

(3) the vaccine is effective in a virus challenge test for a different viral strain (cross-prevention ability) (Example 2, Figs. 3 and 4), and

(4) even by intranasal inoculation, side effects on the central nerve system are unexpectedly absent and safety requirement is satisfied as well (Example 3 and Fig. 5).

Neither Hilleman nor Wong describes virus specific induction of IgA on a mucosal surface or cross strain prevention. Thus, use of a vaccine comprising double stranded RNA and an influenza antigen produces unexpected superior results as compared to Hilleman and Wong. For the foregoing reasons, Applicants respectfully request withdrawal of the rejection of claims 11-14 under 35 U.S.C. § 103(a).

Applicants believe the foregoing remarks are fully responsive to the Office Action. Applicants believe that the claims are in condition for allowance and respectfully request that all outstanding rejections are withdrawn and the application is passed to issuance.

Respectfully submitted,

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